development of diabetes (claims 8-9) or a method employing any CD28 agonist (claim 1).

According to MPEP 2164.01, the test of enablement is whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. Amended claim 1 recites a method for preventing the development of autoimmune diabetes in a susceptible subject by administering an anti-CD28 agonist antibody, a human B7-2 protein, a B7-2 extracellular domain polypeptide, or an effective fragment of said polypeptide. It was well known at the priority date of this application that B7-2 protein and its extracellular domain acted as agonists of the CD28 receptor. This is described at page 7, lines 19 to 31 of the specification as filed.

It is respectfully submitted that disclosure would have been enabling to the artisan at the time of filing, and thus the enablement requirement is satisfied. Withdrawal of this rejection is respectfully requested.

¶6 Claim 1 was rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification allegedly did not describe a sufficient number of CD28 agonists. According to the written description requirement of MPEP 2163, Applicant's specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the presently claimed invention. As noted above, amended claim 1 recites an anti- CD28 co-stimulatory receptor (CD28) agonist antibody, a human B7-2 protein, a B7-2 extracellular domain polypeptide, or an effective fragment of said polypeptide. It is submitted that at the time of filing, Applicant was in possession of the instantly claimed invention. This rejection is now moot. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

¶8 Claims 1-6 and 8-9 were rejected as allegedly unpatentable over Rabinovitch (Diabetes (194), v. 43, pp. 613-621) and Lenschow et al. (Immunity (1996), v. 5, pp. 285-293) in view of either King et al. (Eur. J. Immunol., (1995), v. 25, pp. 587-595) or Webb et al. (Blood (1995), v. 86, pp. 3479-3486).

According to MPEP 2143, to establish a *prima facie* case of obviousness (a) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to the artisan, to modify or combine the references; (b) there must be a reasonable expectation of success; and (c) the cited reference (or references when combined) must teach or suggest all the claim limitations. What is more, the Examiner must step backward in time and into the shoes worn by the hypothetical artisan when the invention was unknown and just before it was made. See MPEP 2142.

It is respectfully submitted that the Examiner is applying impermissible hindsight and selecting the cited references which are consistent with the inventor's findings while ignoring others which are not consistent with the inventor's findings but which would have influenced one of ordinary skill in the art reviewing the available knowledge at the priority date of this application.

In support of Applicant's further arguments set out below, we enclose the Declaration of Dr. Terry L. Delovitch, the inventor herein. It was not possible to obtain a signed copy of the Affidavit in time for submission with this Amendment but a signed copy will follow shortly.

Rabinovitch discusses findings that both specific and non-specific stimulation of the immune system were able to reduce or prevent development of IDDM in NOD mice. It was suggested that non-specific immune stimulation, for example using viral and bacterial materials, could be used to prevent autoimmune diabetes.

By the priority date of this application, however, other workers had attempted to delay or prevent diabetes development in humans by administering bacterial

materials in the form of BCG vaccine. As noted at paragraph 5 of the Delovitch Declaration, these trials were unsuccessful.

There were therefore conflicting findings on the suitability of the type of intervention described by Rabinovitch for preventing diabetes. One of skill in the art would therefore not have had a reasonable expectation of success in preventing diabetes development by immunostimulation or by up-regulating the Th2 arm of the immune response, as suggested by Rabinovitch, as evidenced by the view of Dr. Delovitch at paragraph 6 of his Declaration.

Turning to the Lenschow reference, this reference presents a very confusing picture of the role of the CD28 pathway in the development of IDDM in NOD mice, in that they found that disruption of the CD28 pathway at 0 to 2 weeks led to increased development of IDDM, disruption at 2 to 5 weeks had no effect and disruption at 5 to 7 weeks gave suppression of the disease.

They noted that GAD-specific T cells were able to develop in the absence of CD28 co-stimulation and suggested that this was due to the presence of other co-stimulatory molecules which acted as substitutes in these mice; this is discussed at paragraphs 8 to 10 of the Delovitch Declaration.

In view of the presence of these other co-stimulatory molecules, and in view of the presence of autoantigen-sensitive T cells in the mice studied by Lenschow, one of skill in the art would not have drawn the conclusion drawn by the Examiner, as set out in paragraphs 11 and 12 of the Delovitch Declaration.

The authors of the Lenschow reference do discuss Th1/Th2 balance and advance various theories to try to reconcile their contradictory findings.

It is significant, however, that the authors, who are themselves of skill in the art, came to the following final conclusion, mentioning only CD28 antagonists (p. 291):

> In conclusion, the use of CD28 antagonists to regulate autoimmune diseases may result in distinct outcomes depending on the stage of disease, relative expression of the CD28 ligands, and the genetic predisposition toward Th1 and Th2 subsets.

> Thus, careful manipulation of the CD28/B7 signalling pathway will be necessary to impact reliably upon the course of an autoimmune disease.

It is noteworthy that they do not mention or consider anywhere in the paper the use of CD28 agonists. It clearly did not occur to them that CD28 agonists would be useful to treat IDDM.

At the priority date of the subject application, one of skill in the art would not have had a reasonable expectation of success in treating or preventing autoimmune diabetes by immune stimulation. Rabinovitch's reported indications were offset by the known failure of attempts such as BCG vaccination to have any ameliorative effect on diabetes development. It was also known that immunosuppression was well recognised as a diabetes-preventive, as acknowledged by Rabinovitch (page 613, column 2).

Furthermore, for the reasons clearly set out in the accompanying Declaration of Dr. Terry Delovitch, one of skill in the art would not have had a reasonable expectation, based on Lenschow's teachings of the effect of disruption of the CD28 pathway, that stimulation of the CD28 pathway would be of assistance in preventing autoimmune diabetes.

One of skill in the art who wished to prevent the development of autoimmune diabetes would therefore have had no motivation to look for a method of immune stimulation or of up-regulating Th2 cells, or a method to stimulate the CD28 pathway. He or she would therefore have had no motivation to apply the antibodies of King et al. or Webb et al. to the problem of diabetes prevention.

CONCLUSION

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

For the Examiner's convenient reference, attached hereto is a reproduction of the claims presently under examination, captioned "**Claims presently under examination.**"

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

Nathan S. Cassell
Reg. No. 42,396

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
NSC:nsc

Enclosures
- Declaration of Terry L. Delovitch
- Curriculum Vitae of Terry L. Delovitch
- Dahlquist et al., Diabetologia, 38(7):873-874 (1995)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 2, 3, and 8 have been canceled, and claims 1, 4, 5, and 9 have been amended as follows.

1. (Twice Amended) A method for preventing the development of **[an]** autoimmune diabetes **[disease associated with increased Th1 immune cell activity]** in a susceptible subject comprising administering to the subject an effective amount of **[a T cell]** an anti-CD28 costimulatory receptor (CD28) agonist antibody, a human B7-2 protein, a B7-2 extracellular domain polypeptide, or an effective fragment of said polypeptide.

2-3. Canceled

4. (Amended) The method of claim **[3]** 1 wherein the **[agonist]** administered substance is an anti-CD28 agonist antibody.

5. (Amended) The method of claim **[4]** 1 wherein the subject is a human subject.

8. Canceled

9. (Twice Amended) The method of claim **[8]** 5 wherein the human subject is aged from about 6 months to about 2 or **[three]** 3 years.

CLAIMS PRESENTLY UNDER EXAMINATION.

1. (Twice Amended) A method for preventing the development of autoimmune diabetes in a susceptible subject comprising administering to the subject an effective amount of an anti- CD28 co-stimulatory receptor (CD28) agonist antibody, a human B7-2 protein, a B7-2 extracellular domain polypeptide, or an effective fragment of said polypeptide.

2-3. Presently Canceled

4. (Amended) The method of claim 1 wherein the administered substance is an anti-CD28 agonist antibody.

5. (Amended) The method of claim 1 wherein the subject is a human subject.

6. The method of claim 5, wherein the antibody is a monoclonal antibody.

7. Previously Canceled

8. Presently Canceled

9. (Twice Amended) The method of claim 5 wherein the human subject is aged from about 6 months to about 2 or 3 years.

10-31. Previously Canceled